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Intrahepatic cholestasis of pregnancy

Authors: Keith D Lindor, MD, Richard H Lee, MD
Section Editors: Charles J Lockwood, MD, MHCM, Sanjiv Chopra, MD, MACP
Deputy Editors: Kristen M Robson, MD, MBA, FACG, Vanessa A Barss, MD, FACOG

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INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is characterized by pruritus and an elevation in serum bile acid concentrations, typically developing in the late second and/or third trimester and rapidly resolving after delivery. The major clinical features, diagnosis, and management of ICP will be reviewed here. A general approach to the pregnant woman who develops liver disease is presented elsewhere. (See "Approach to liver disease occurring during pregnancy".)

INCIDENCE AND EPIDEMIOLOGY

ICP is the most common liver disease unique to pregnancy [1]. The reported incidence of ICP varies widely worldwide, ranging from <1 to 27.6 percent, for reasons that are incompletely understood [2,3]. Geographic variations may reflect differences in susceptibility between ethnic groups, as well as differences in environmental factors [4,5]. In the United States, incidence rates range from 0.32 percent in Bridgeport Hospital, Connecticut [6] to 5.6 percent in a primarily Hispanic population in Los Angeles [7]. Across Europe the incidence ranges from 0.5 to 1.5 percent, with the highest rates in Scandinavia [2]. The incidence is 1.2 to 1.5 percent in Indian-Asians and Pakistani Asians [8]. The Araucanos Indians in Chile have the highest incidence worldwide at 27.6 percent [4].

For unknown reasons, the disease occurs more commonly in the winter months in some countries (eg, Sweden, Finland, Chile) [2]. It is more common in multiple gestations (twins 20.9 versus singletons 4.7 percent in one study from Chile [9]; triplets 43 percent versus twins 14 percent in one study from Finland [10]). Other epidemiologic factors include chronic hepatitis C, prior history or family history of intrahepatic cholestasis, and advanced maternal age [11].

Women with a past history of ICP frequently have ICP in subsequent pregnancies. (See 'Recurrence in subsequent pregnancies' below.)

ETIOLOGY

The etiology of ICP is not completely understood, but likely involves a combination of genetic susceptibility, hormonal factors, and environmental factors.

Genetic susceptibility — The genetic basis of ICP is complex, but genetic susceptibility to the disorder is supported by evidence of familial clustering, increased risk in first-degree relatives, increased risk in some ethnic groups, and a high (60 to 70 percent) recurrence rate (see 'Recurrence in subsequent pregnancies' below) [12].

The *ABCB4* (adenosine triphosphate-binding cassette, subfamily B, member 4) gene encoding the multidrug resistance 3 (MDR3) protein (a canalicular phospholipid translocator) is primarily involved in a subtype of progressive familial intrahepatic

cholestasis called PFIC3 [13]. Heterozygous mutations in *ABCB4* (also called *MDR3*) have been found in a large consanguineous family in whom some women had episodes of cholestasis during pregnancy [14,15]. Several heterozygous mutations in the *ABCB4* gene were subsequently reported in patients with ICP [16-21]. The prevalence of such *ABCB4* gene mutations in Caucasian patients with ICP is 16 percent [22].

Some genes encoding for other canalicular transporters or their regulators may also be involved in ICP pathogenesis (eg, *ABCB11, ATP8B1, ABCC2, NR1H4*) [23-26].

Estrogen and progesterone — A role for estrogen in ICP is supported by evidence that estrogen causes cholestasis in both experimental and clinical conditions: ICP occurs mainly in the second half of pregnancy when serum concentrations of estrogen reach peak levels; ICP is more common in twin pregnancies, which are associated with higher levels of circulating estrogen than singleton pregnancies; cholestasis occurs in women taking estrogen-progestin contraceptives; ICP has been reported in early pregnancy after ovarian hyperstimulation, which results in markedly high serum estrogen levels; and ICP resolves after delivery of the placenta, which was a major source of estrogen production across the second and third trimesters [9,27,28].

Alterations in progesterone metabolism may also play a role in the pathogenesis of ICP. In some genetically predisposed women, the formation of large amounts of sulfated progesterone metabolites in pregnancy, possibly related to greater 5-alpha and 3-alpha reduction, may result in saturation of the hepatic transport system(s) utilized for biliary excretion of these compounds [29,30]. Pregnancy also decreases sulfotransferase activity [31]. Whether administration of exogenous progesterone during pregnancy further increases the risk of ICP is unknown. In placebo-controlled randomized trials of progesterone supplementation for reducing the risk of spontaneous preterm birth, an increased frequency of ICP has not been specifically reported, but the package insert for hydroxyprogesterone caproate (Makena) describes an 8 percent incidence of pruritus in treated women and lists cholestatic jaundice of pregnancy, liver tumors (benign or malignant), or active liver disease as contraindications to therapy [32]. (See 'Special populations' below.)

Environmental factors — The seasonal and geographic variability in ICP suggest that environmental factors could modulate the expression of the disease [3]. (See 'Incidence and epidemiology' above.)

Specific causal factors in the environment have not been identified, but low selenium levels due to diet and low vitamin D levels due to lack of exposure to sunlight have been implicated [11,33].

Underlying liver disease — A small subset of women with ICP has identifiable underlying liver disease [34-37]. A large population-based study found an association between ICP and several chronic liver diseases, such as hepatitis C and nonalcoholic liver cirrhosis [35]. Progressive fibrosis was also reported in four sisters who had an atypical familial form of prolonged recurrent intrahepatic cholestasis during pregnancy [36]. This suggests that some women who develop ICP have underlying liver disease revealed by pregnancy or contributing to the development of ICP.

CLINICAL FINDINGS

Presentation — The onset of ICP is typically heralded by the development of pruritus, which ranges from mild to intolerable. It is often generalized, but generally starts and predominates on the palms and soles and is worse at night. Right upper quadrant pain, nausea, poor appetite, sleep deprivation, or steatorrhea may occur.

Pruritus and other symptoms usually develop during the late second or third trimester. Transient first trimester symptoms have been linked to ovarian hyperstimulation syndrome after in vitro fertilization [28], while persistent and worsening symptoms are characteristic of naturally conceived pregnancies [38].

Encephalopathy or other stigmata of liver failure, if present, should initiate a search for other causes of liver disease. (See "Approach to liver disease occurring during pregnancy".)

Physical examination — Physical examination may show scratch marks, excoriations, and prurigo nodules secondary to scratching, but no primary skin lesions are associated with the disease. Jaundice occurs in 14 to 25 percent of patients, typically developing one to four weeks after the onset of itching [39]. Jaundice without pruritus is rare and should prompt investigation of other causes.

Laboratory findings — An increase in serum total bile acid concentration is the key laboratory finding (present in >90 percent of affected pregnancies), and may be the first and only laboratory abnormality [32,40,41]. Pruritus may precede laboratory abnormalities [42].

Other potential laboratory abnormalities include increases in:

- Serum aminotransferases (elevated in 60 percent of cases), which are usually less than two times the upper limit of normal, but may reach values greater than 1000 unit/L, making distinction from viral hepatitis important [32].
- Alkaline phosphatase, which may be elevated fourfold but is not specific for cholestasis during pregnancy due to expression of the placental isoenzyme.
- Total and direct bilirubin concentrations (elevated in 25 percent of cases), although total bilirubin levels rarely exceed 6 mg/dL.

The serum concentration of gamma-glutamyl transpeptidase (GGT) is normal or modestly elevated (30 percent of cases), which is unusual in most other forms of cholestatic liver disease in which GGT levels parallel other cholestatic markers.

The prothrombin time is usually normal. When prolonged, it is typically secondary to vitamin K deficiency from fat malabsorption due to severe steatorrhea or secondary to use of bile acid sequestrants (such as cholestyramine), rather than liver dysfunction. However, steatorrhea is usually modest, and nutritional requirements are generally easily met [43].

The primary bile acids are cholic and chenodeoxycholic acids, which are conjugated with glycine or taurine before being secreted into the bile. Cholic and chenodeoxycholic acid levels are increased, but cholic acid increases more than chenodeoxycholic acid, resulting in a marked elevation of the cholic/chenodeoxycholic acid ratio compared with pregnant women without ICP (3.4 versus 1.1) [39,44,45]. However, most women with an elevated bile acid ratio also have elevated total bile acid levels; as a result, obtaining a ratio does not enhance diagnostic performance [46]. The ratio of glycine/taurine conjugates of bile acids is decreased (<1). (See "Tests of the liver's capacity to transport organic anions and metabolize drugs".)

Ultrasonography — ICP is not associated with abnormalities on imaging (biliary ducts are not dilated, hepatic parenchyma appears normal).

Pathology — Histopathology is characterized by cholestasis without inflammation [47]. Bile plugs in hepatocytes and canaliculi predominate in zone 3. The portal tracts are unaffected. However, histopathology is rarely available as liver biopsy is not necessary for diagnosis.

DIAGNOSIS

The diagnosis of ICP is based upon the presence of pruritus associated with elevated total serum bile acid levels, elevated aminotransferases, or both and the absence of diseases that may produce similar laboratory findings and symptoms. Although some variation in laboratory criteria exists among guidelines [48], severe cholestasis is consistently defined as bile acids over 40 micromol/L, and accounts for about 20 percent of cases.

Aminotransferase levels are not affected by pregnancy. The laboratory's pregnancy-specific reference ranges for total serum bile acids in each trimester, if available, should be used to determine whether the level is elevated. Otherwise, the laboratory's cut-off for the general population is used. Total serum bile acid cut-off levels reported in the literature vary

because of differences in laboratory methods, fasting status, population studied, and gestational age at diagnosis [49]. Postprandial serum total serum bile acid levels are generally higher than fasting levels [50].

Because pruritus can precede the rise in serum bile acids by several weeks, we suggest repeating laboratory tests weekly if total bile acid and aminotransferase levels are initially normal. However, if ursodeoxycholic acid is started empirically, elevated bile acid and transaminase levels may never be detected. (See 'Ursodeoxycholic acid' below.)

Diagnostic evaluation and differential diagnosis — History, physical examination, and laboratory evaluation are performed to rule-in the diagnosis and rule-out other disorders in differential diagnosis. Laboratory studies should include:

- Total serum bile acid concentration
- Serum aminotransferases (alanine aminotransferase and aspartate aminotransferase)

The differential diagnosis of pruritus and hepatic dysfunction in pregnancy are addressed in the table (table 1). There are multiple causes of abnormal liver biochemical and function tests; the detailed evaluation of patients with these abnormalities is reviewed separately. (See "Approach to the patient with abnormal liver biochemical and function tests".)

Pruritus affects 23 percent of pregnancies, but only a small proportion are due to ICP [51]. Pruritus, the cardinal feature of ICP, helps distinguish ICP from other types of pregnancy-related disorders characterized by elevated transaminase levels (eg, HELLP syndrome, preeclampsia with severe features, acute fatty liver of pregnancy). However, ICP has been associated with development of preeclampsia [52-54] and acute fatty liver of pregnancy [55]. The lack of primary skin lesions in ICP helps to differentiate it from most pregnancy-specific pruritic dermatoses and skin conditions unrelated to pregnancy. (See "Maternal adaptations to pregnancy: Skin, hair, nails, and mucous membranes", section on 'Pruritus' and "Pruritus: Etiology and patient evaluation".)

FETAL EFFECTS

Morbidity and mortality — Maternal bile acids cross the placenta and can accumulate in the fetus and amniotic fluid, which carries significant risk for the fetus [32,56]. Transplacental gradients facilitate fetal clearance of bile acids in normal pregnancies, but are reversed in cholestatic pregnancies, which causes accumulation of bile acids in the fetus and amniotic fluid [57].

The main complications are increased risks for intrauterine demise, meconium-stained amniotic fluid, preterm delivery (spontaneous and iatrogenic), and neonatal respiratory distress syndrome (which appears to be associated with bile acids entering the lungs) [58,59]. The magnitude of these risks was described in a systematic review and individual patient data meta-analysis comparing pregnancy outcomes in ICP versus the general obstetric population [59]:

- Stillbirth (0.91 versus 0.32 percent; OR 1.46, 95% CI 0.73–2.89)
- Spontaneous preterm birth (13.4 versus 4.0 percent; OR 3.47, 95% CI 3.06-3.95)
- Iatrogenic preterm birth (OR 3.65, 95% CI 1·94–6·85)
- Meconium stained amniotic fluid (18.7 versus 10.8 percent; OR 2.60, 95% CI 1.62-4.16)
- NICU admission (OR 2.12, 95% CI 1.48-3.03)

The risk of fetal demise increased with higher serum total bile acid levels, especially ≥100 micromol/L:

- <40 micromol/L (0.13 percent)
- 40 to 99 micromol/L (0.28 percent; hazard ratio 2.35, 95% CI 0.52-10.50 compared with <40 micromol/L)
- ≥100 micromol/L (3.44 percent; hazard ratio 30.50, 95% CI 8.83–105.30 compared with <40 micromol/L)

Only women with total bile acids ≥100 micromol/L at any point in their pregnancy had stillbirth rates statistically significantly higher than the pooled national stillbirth rate (0.3 to 0.4 percent). The rate of stillbirth in these pregnancies increased with increasing gestational age, particularly beyond 34 to 36 weeks. Because most patients in this study with ICP were delivered by 40 weeks, the hazard ratios were calculated only to 39 weeks of gestation.

Although there was no increase in stillbirth compared with the background population risk before 39 weeks of gestation for those patients with total bile acids <100 micromol/L, this effect is likely due to the role of early delivery for patients with ICP, as demonstrated by the high iatrogenic preterm birth rate. These data suggest that with contemporaneous management of ICP (eg, early delivery, ursodeoxycholic acid (UDCA), fetal monitoring), the risk of stillbirth is reduced to the background population risk for those with total bile acids <100 micromol/L, but not in patients who have total bile acids ≥100 micromol/L. (See 'Pregnancy management' below.)

Although some patients received UDCA, the available data were not sufficient for determining whether treatment with UDCA reduced the stillbirth rate.

The pathophysiology of fetal death in ICP is poorly understood, but may be related to the sudden development of a fetal arrhythmia [60] or vasospasm of the placental chorionic surface vessels [61] induced by high levels of bile acids. Coexistent pregnancy complications (eg, gestational diabetes, preeclampsia) may also play a role [62].

Pregnancies complicated by spontaneous preterm birth appear to have earlier onset of pruritus [63]. Bile acids appear to increase expression of myometrial oxytocin receptors, which may explain the increase in spontaneous preterm labor [64,65].

Fetal growth restriction and oligohydramnios are not features of the disease [32].

MATERNAL TREATMENT

Goals — The management of ICP has two main goals:

- Reducing bothersome symptoms
- Reducing the risk of perinatal morbidity and mortality

Although pruritus is bothersome, ICP is not associated with other serious maternal sequelae.

Candidates for treatment — We offer treatment to all patients with ICP. (See 'Diagnosis' above.) For patients with characteristic clinical symptoms (see 'Presentation' above) but normal serum bile acid and aminotransferase levels, either empiric treatment may be initiated or laboratory tests can be repeated weekly with initiation of treatment once the total bile acid or serum transaminase levels or both are elevated.

Ursodeoxycholic acid

Administration and outcome — Ursodeoxycholic acid (UDCA) is the preferred treatment of ICP [66]. UDCA results in complete resolution of pruritus in approximately 42 percent of patients and an improvement in pruritus in approximately 61 percent [67]. In addition, it improves laboratory abnormalities associated with ICP, may improve perinatal outcome, and has no known fetal/neonatal toxicity [67-69].

The optimal starting dose has not been determined; we usually prescribe 300 mg three times a day (or 15 mg/kg per day) until delivery, but 300 mg twice daily (or 10 mg/kg per day) is also reasonable [48]. The drug is well-tolerated by most patients, but mild nausea and dizziness have been reported in up to 25 percent of patients.

A decrease in pruritus is usually seen within one to two weeks, and biochemical improvement is usually seen within three to four weeks. If pruritus is not relieved to a tolerable level within about two weeks, the dose is titrated every week or two to symptoms [70], to a maximum dose of 21 mg/kg per day [71-73].

Meta-analyses support efficacy of UDCA [67-69]. In a meta-analysis of 12 randomized trials including a total of 662 patients [68], patients with ICP who received UDCA had better outcomes than those who received an alternative agent (eg, S-adenosyl-methionine, cholestyramine, or placebo) [69]:

- Resolution of pruritus (risk ratio 1.68, 95% CI 1.12-2.52)
- Reduction in alanine aminotransferase levels (standardized mean difference (SMD) -1.36; 95% CI -2.08 to -0.63)

- Reduction in bile acid levels (SMD -0.68; 95% CI -1.15 to -0.20)
- Reduction in premature birth (RR 0.56, 95% CI 0.43-0.72)
- Reduction in fetal distress (RR 0.68; 95% CI 0.49-0.94)
- Reduction in respiratory distress syndrome (RR 0.33, 95% CI 0.13-0.86)
- Reduction in neonatal intensive care unit admission (RR 0.55, 95% CI, 0.35-0.87)
- Increased gestational age (SMD 0.44, 95% CI 0.26-0.63) and birth weight (SMD 0.21, 95% CI 0.02-0.40)

Although long-term outcome was not evaluated in the meta-analysis, a study of children exposed to UDCA in utero and examined at 1 to 12 years of age reported all were healthy [74]. Although meta-analyses support the efficacy of UDCA, they are limited by small numbers of patients and adverse fetal events; heterogeneity in patient populations, interventions, and assessed outcomes; and moderate to high risk of bias [67-69].

Pretreatment and posttreatment laboratory monitoring — We do not obtain any additional laboratory tests before starting treatment, other than those used to make the diagnosis of ICP.

Serial re-evaluation (weekly) of maternal total serum bile acid concentrations is recommended due to the significantly increased risk of stillbirth in patients with total bile acid concentrations ≥100 micromol/L [59]. Clinical decision making is based on the highest total bile acid level at any point during the pregnancy, maternal obstetrical history, and symptoms. Thus, we would not increase the UDCA dose to reduce elevated laboratory results if pruritus has been relieved and we would not revise the planned time of delivery if laboratory abnormalities improve (see 'Timing of delivery' below).

Postpartum, total bile acids and transaminases are rechecked to make sure biochemical improvement has occurred. (See 'Follow-up' below.)

Refractory cases — If the maximum dose of UDCA is reached and pruritus remains intolerable, one of the following drugs can be added.

- **S-adenosyl-methionine** – The glutathione precursor S-adenosyl-methionine (SAMe) influences the composition and fluidity of hepatocyte plasma membranes and increases the methylation and biliary excretion of hormone metabolites [75]. In a meta-analysis of five randomized trials including 311 pregnant patients, UDCA 450 to 1000 mg/day decreased the pruritus score, total bile acids, and alanine aminotransferase levels more effectively than SAMe 800 to 1000 mg/day [76]. It is usually administered intravenously, which is inconvenient as prolonged therapy is required. Oral SAMe (1600 mg/day) has been used to treat cholestasis in nonpregnant patients [77].

- Cholestyramine – Cholestyramine decreases ileal absorption of bile salts, thereby increasing their fecal excretion. Cholestyramine is given orally in divided doses starting at 2 to 4 g per day and gradually increased to a maximum dose of 16 g per day, if needed for symptom control [78]. However, its effect on pruritus in ICP is limited and cholestyramine may cause constipation, abdominal discomfort, and malabsorption of fat including fat-soluble vitamins (eg, vitamin K), especially at high doses (eg, >4 grams per day).

- Rifampin **(also known as rifampicin)** – Rifampin is a potent agonist of the pregnane X receptor (PXR), which mediates many detoxification and hepatobiliary processes. It relieves pruritus in nonpregnant patients with pruritus associated with cholestasis, but potential adverse effects include nausea, decreased appetite, hemolytic anemia, renal failure, and hepatitis. (See "Pruritus associated with cholestasis", section on 'Rifampin'.)

  Experience with combined use with UDCA for treatment of refractory ICP is limited to fewer than 30 patients [79,80]. In these cases, the total daily dose of rifampin ranged from 300 to 1200 mg, administered in divided doses. Pruritus improved in most patients (11/16) and many had a reduction in bile acid and/or transaminase levels. All of the infants were delivered between about 32 and 37 weeks, with good perinatal outcomes.

Other drugs — Alternative drugs may be considered in patients who are unable to take UDCA, but none have comparable efficacy [67-69].

Hydroxyzine 25 mg every six to eight hours or chlorpheniramine 4 mg every four to six hours has been used to treat pruritus with minimal efficacy, but provides sedation at night. Calamine lotion or aqueous cream with 2 percent menthol may also relieve pruritus. No trials have been performed in women with ICP and none of these therapies improves laboratory abnormalities.

In a randomized trial of 130 women with ICP, dexamethasone 12 mg per day did not improve pruritus or reduce the serum aminotransferase levels, and was less effective than UDCA 1000 mg/day at reducing bilirubin and bile acids [81].

Other treatments, including charcoal, ultraviolet light, herbal remedies, and phenobarbital, have been used, but few patients have been treated and with uncertain efficacy.

PREGNANCY MANAGEMENT

Antepartum fetal assessment — We follow all pregnancies with ICP with twice weekly modified biophysical profiles, although the value of antepartum fetal testing to identify fetuses at risk of demise in the setting of ICP is unproven [82]. One study did not observe an increase in abnormal findings on nonstress tests (NSTs) in patients with ICP who went on to have a fetal demise [82]. Several others reported intrauterine fetal demise occurring within a few days of a reactive NST [83-89].

Nonstress tests and other tests (biophysical profile score, daily fetal kick count) for detection of the effects of chronic placental insufficiency on the fetus may not be useful in ICP because the mechanism of intrauterine fetal demise is thought to be a sudden event rather than the result of a chronic placental vascular process. However, in the absence of high-quality evidence of the lack of value of fetal testing or a proven mechanism for fetal death, many obstetricians order antepartum testing in women with ICP to detect the rare test suggesting fetal compromise and the need for immediate delivery [1,86,88]. (See "Overview of antepartum fetal surveillance".)

Timing of delivery

Our approach — We favor early delivery to reduce the risk of fetal demise and to initiate disease resolution. The timing should be guided by balancing the risk of fetal death with expectant management against the potential risks of prematurity with early delivery. (See "Short-term complications of the preterm infant" and "Late preterm infants".)

We deliver most women with ICP at 36+0 to 36+6 weeks of gestation or upon diagnosis if ICP is diagnosed at ≥37+0 weeks of gestation, without performing an amniocentesis to check fetal pulmonary maturity prior to delivery. Our approach is based on data from a retrospective cohort study that sought to determine the risk of perinatal mortality (stillbirth plus infant death) with delivery versus expectant management stratified by gestational age week between 34 and 40 weeks of gestation [90]. Over 1.6 million pregnancies in women with and without ICP (based on ICD-9 codes) who delivered in California between 2005 and 2008 were analyzed. In women with ICP, fetal, neonatal, or infant mortality was lowest (4.7 deaths per 10,000 fetuses at risk, 95% CI 0.0-10.5) with delivery at 36 weeks and substantially lower than mortality with expectant management at 36 weeks (19.2 per 10,000 fetuses at risk, 95% CI 7.6-30.8). The lower mortality with delivery versus expectant management was also observed at 37 weeks (12.3 versus 21.7 per 10,000 fetuses at risk), 38 weeks (13.7 versus 23.1 per 10,000 fetuses at risk), and 39 weeks (18.3 versus 33.6 per 10,000 fetuses at risk). Limitations of the study were that no information was available on maternal bile acid and transaminase levels, gestational age at onset of disease, or treatment, and the small number of deaths.

We consider delivery prior to 36 weeks of gestation in women with ICP and:

- Excruciating and unremitting maternal pruritus not relieved with pharmacotherapy.
- Jaundice.
- A prior history of fetal demise before 36 weeks due to ICP with recurring ICP in the current pregnancy.
- High total serum bile acid concentration ≥100 micromol/L [59,91,92] (determination of bile acid concentrations may take several days even in major laboratories, making it an impractical tool for immediate risk stratification [93]).

The timing of delivery in these situations is empirical and generally delayed as long as possible after 34 weeks of gestation, depending on the individual patient's particular circumstances (severity of symptoms, gestational age of previous fetal demise, values and preferences). All patients electively delivered for ICP prior to 36 weeks are extensively counseled about the absence of definitive evidence that the maternal and fetal benefits of ending the pregnancy outweigh the potential morbidity of prematurity. We also discuss the limits of fetal lung maturity testing for prediction of neonatal status. If the patient chooses to be delivered after this discussion, we offer a course of antenatal corticosteroids and proceed with delivery. (See "Antenatal corticosteroid therapy for reduction of neonatal respiratory morbidity and mortality from preterm delivery", section on '34+0 or more weeks'.)

Recommendations of others

- The Royal College of Obstetricians and Gynecologists guideline on ICP states available data may justify offering women induction of labor after 37+0 weeks of pregnancy, particularly those with more severe biochemical abnormalities [94]. However, the rationale for this recommendation versus our recommendation for earlier delivery is unclear since they also state that "in over 1500 actively managed obstetric cholestasis pregnancies, most of which were diagnosed before 37 weeks of gestation, 13 of 18 stillbirths occurred before 37 weeks of gestation and five were at 37 to 38 weeks of gestation." Moreover, they state that in one study "227 women suffered 20 fetal deaths in singleton pregnancies, of which 18 were over 37 weeks of gestation."

- The Society for Maternal-Fetal Medicine states "while an evidence based recommendation is not available for the timing of delivery when cholestasis of pregnancy is encountered, most management strategies would advocate delivery between 37 and 38 weeks or sooner with documented pulmonary maturity." Prior obstetrical history, antenatal testing, and gestational age should be considered" [95]. This opinion was based on three studies suggesting that this strategy results in perinatal outcomes similar to those in pregnancies not complicated by ICP [56,96,97]. Although the SMFM also cited a study supporting expectant management of mild ICP (bile acids <40 micromol/L) [98], they did not consider bile acid level in their guidance.

- The American College of Obstetricians and Gynecologists recommends delivery at 36+0 to 37+0 weeks of gestation, or at diagnosis if diagnosed at term [99]. However, earlier delivery may be indicated depending on clinical circumstances.

Delivery — No special considerations related to delivery are required in women with ICP. Continuous fetal monitoring during labor is indicated, given increased frequency of fetal death and non-fatal asphyxial events [98,100]. Labor induction does not necessarily lead to an increased risk of cesarean delivery compared with expectant management. (See "Techniques for ripening the unfavorable cervix prior to induction" and "Induction of labor with oxytocin".)

There does not appear to be an increased risk for postpartum hemorrhage when ICP is managed with UDCA [43]. Therefore, we do not routinely assess coagulation parameters or prescribe vitamin K before delivery. In rare refractory cases, the prothrombin time can be checked and vitamin K administered if it is prolonged [101,102].

MATERNAL OUTCOME

Postpartum course — Pruritus usually disappears in the first few days following delivery, accompanied by normalization of serum bile acid concentrations and other liver tests [32].

Breastfeeding — ICP is not a contraindication to breastfeeding. UDCA is discontinued when labor begins. Low levels of ursodeoxycholic acid have been found in breast milk, thus only small amounts will be ingested by the infant and are not expected to cause any adverse effects in breastfed infants [103].

Follow-up — We check liver biochemical tests and bile acid concentration six to eight weeks after delivery to confirm that previously noted abnormalities have resolved. If laboratory abnormalities do not return to normal, the patient should be referred to a hepatologist to assess for underlying hepatobiliary diseases.

Studies suggest that ICP may be associated with subsequent diagnosis of gallstone disease, hepatitis C, fibrosis, cholangitis, hepatobiliary cancer, immune-mediated disease, and cardiovascular disease [34,35,104,105]. In a Swedish registry-based study including over 11,000 postpartum women who had ICP matched with over 113,000 women who gave birth but did not have ICP, ICP was associated with the subsequent development of liver or biliary tract cancer (hazard ratio [HR] 3.6; 95% CI 1.7-7.8 and HR 2.6; 95% CI 1.3-5.5, respectively), diabetes mellitus (HR 1.5; 95% CI 1.3-1.7), thyroid disease (HR 1.3; 95% CI 1.1-1.5), Crohn disease (HR 1.6; 95% CI 1.1-2.1), and cardiovascular disease (HR 1.1; 95% CI 1.1-1.2) [105]. The increased risk for cardiovascular disease was only in those women with ICP who also had preeclampsia, which is a known risk factor. (See "Preeclampsia: Management and prognosis", section on 'Cardiovascular disease'.)

Recurrence in subsequent pregnancies — Cholestasis recurs during subsequent pregnancies in 60 to 70 percent of women with ICP. Recurrent episodes are variable in severity compared with the index pregnancy.

Contraception — Any nonhormonal contraceptive may be used. Issues related to hormonal contraception are discussed below.

Estrogen-progestin — The administration of estrogen-progestin contraceptives to women with a history of ICP rarely results in recurrent cholestasis. Thus, combined hormonal contraceptives can be initiated after normalization of liver function tests. However, women should be informed of the possible development of pruritus or cholestasis, which should prompt discontinuation of the combined hormonal contraceptive. We also routinely check liver function tests after three or six months of such contraception.

The Centers for Disease Control and Prevention consider estrogen-progestin contraception an acceptable choice for women with a past history of ICP since the benefits generally outweigh the risks [106]. However, in women with cholestasis related to past use of estrogen-progestin contraceptives, non-estrogen methods of contraception are preferred due to the increased risk for recurrent cholestasis.

Progestin-only — The Centers for Disease Control and Prevention consider progestin-only contraceptives an acceptable choice for women with a history of ICP or cholestasis related to use of estrogen-progestin contraceptives [106]. The risk of recurrent cholestasis is low.

SPECIAL POPULATIONS

- Women with a history of cholestasis undergoing ovarian stimulation for in vitro fertilization may experience transient symptoms of cholestasis related to transiently high estrogen levels, but data regarding the frequency of this phenomenon are sparse and limited to case reports [27]. General recommendations for changes in standard ovarian stimulation protocols are not warranted for such women at this time.
- Progesterone supplementation is often prescribed to women with a history of previous preterm birth or a short cervical length in the current pregnancy. It is uncertain whether to avoid progesterone supplementation in women with a previous history of ICP. We make this decision with the patient after discussing individual risks and benefits, including consideration of her risk of preterm birth in the current pregnancy, the likely gestational age of a recurrent preterm birth with or without progesterone supplementation, and the risk and possible sequelae of recurrent ICP. If she decides to take progesterone, we would discontinue it if she develops ICP. (See "Progesterone supplementation to reduce the risk of spontaneous preterm birth" and 'Estrogen and progesterone' above.)

SUMMARY AND RECOMMENDATIONS

- ICP is characterized by pruritus and an elevation in serum bile acid levels, typically developing in the second and/or third trimester and rapidly resolving after delivery. Pruritus, which may be intolerable, is often generalized but predominates on the palms and the soles of the feet and is worse at night. (See 'Clinical findings' above.)

- The diagnosis of ICP is based upon the presence of pruritus associated with elevated total serum bile acid levels, elevated aminotransferases, or both, and the absence of diseases that may produce similar laboratory findings and symptoms. Severe cholestasis is defined as bile acids over 40 micromol/L, and accounts for about 20 percent of cases. (See 'Diagnosis' above.)

- Pruritus can precede the rise in serum bile acids by several weeks. However, if ursodeoxycholic acid is started empirically, elevated bile acid and transaminase levels may never be detected. (See 'Diagnosis' above.)

- The differential diagnosis of pruritus and hepatic dysfunction in pregnancy are addressed in the table (table 1). Pruritus, the cardinal feature of ICP, helps distinguish ICP from other types of pregnancy-related disorders characterized by elevated transaminase levels (eg, HELLP syndrome, preeclampsia with severe features, acute fatty liver of pregnancy). The lack of primary skin lesions in ICP helps to differentiate it from most pregnancy-specific pruritic dermatoses and skin conditions unrelated to pregnancy. (See 'Diagnostic evaluation and differential diagnosis' above.)

- The major complications of ICP are fetal/neonatal: increased risk for intrauterine demise, meconium-stained amniotic fluid, preterm delivery (spontaneous and iatrogenic), and neonatal respiratory distress syndrome (which appears to be associated with bile acids entering the lungs. (See 'Morbidity and mortality' above.)

- High serum total bile acid concentration (bile acid level ≥100 micromol/L) is associated with a significantly higher risk of stillbirth. We recommend re-checking the total serum bile acid concentration at least weekly for all patients with ICP, and basing management on the highest total serum bile concentration at any time during the pregnancy. (See 'Morbidity and mortality' above and 'Our approach' above.)

- The goal of treatment is to relieve pruritus and possibly prevent fetal complications. If ICP is diagnosed at ≥37 weeks of gestation, we initiate delivery upon diagnosis. Before term, we suggest treatment with ursodeoxycholic acid (ursodiol or UDCA, a synthetic bile acid) (**Grade 2B**). UDCA relieves pruritus in about 70 percent of patients, may improve perinatal outcome, improves laboratory abnormalities associated with ICP, has no known fetal/neonatal toxicity UDCA, and is well-tolerated. The optimal dose has not been determined; 300 mg two or three times a day until delivery is reasonable. (See 'Maternal treatment' above.)

- We deliver most women diagnosed with ICP before term at 36 weeks of gestation, with earlier delivery in complicated cases. (See 'Timing of delivery' above.)

- Liver function and bile acid concentration levels should be checked six to eight weeks after delivery. If these do not return to normal, the patient should be referred to a liver specialist to assess for underlying hepatobiliary diseases. Affected women may be at increased risk for the development of gallstones. (See 'Maternal outcome' above.)

- Cholestasis recurs during subsequent pregnancies in 60 to 70 percent of patients. Recurrent episodes are variable in severity. (See 'Recurrence in subsequent pregnancies' above.)

- ICP is not a contraindication for breastfeeding. (See 'Maternal outcome' above.)

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Diagnosis of intrahepatic cholestasis of pregnancy

Differential diagnosis	Typical clinical presentation	Distinguishing features
Pregnancy-specific causes of pruritus		
Pruritus gravidarum	Pruritus, usually in the third trimester	Similar presentation to intrahepatic cholestasis of pregnancy, but normal liver function tests and bile acids
Atopic eruption of pregnancy	Pruritus, usually in the first trimester	Dry, red rash with or without small blisters Typically affects trunk and limb flexures
Polymorphic eruption of pregnancy	Pruritus, usually in the third trimester	Typically affects lower abdominal striae with umbilical-sparing Urticarial papules or plaques, vesicles, and target lesions
Pemphigoid gestationis	Itchy rash, usually in the second or third trimester	Rare autoimmune condition characterized by complement-fixing immunoglobulin G antibodies Rash develops into large, tense blisters Associated with increased risk of preterm delivery and SGA Recurs in subsequent pregnancies and with combined oral contraceptive
Prurigo of pregnancy	Pruritus, usually in the third trimester	Groups of red-brown papules on the abdomen and extensor surfaces of the limbs Papules may persist postpartum
Pruritic folliculitis of pregnancy	Pruritus, usually in the third trimester	Acneiform eruption on the shoulders, upper back, thighs, and arms Follicular papules and pustules, which may be filled with pus, but culture is typically sterile; rash usually improves with advancing gestation
Preexisting causes of pruritus		
Atopic dermatitis	Pruritus, any gestation	History of atopy
Allergic or drug reaction	Pruritus, any gestation	History of exposure to allergen or drug Maculopapular rash
Systemic disease	History of liver, renal, or thyroid disease	Signs and symptoms of systemic disease History of pruritus before conception
Pregnancy-specific causes of hepatic impairment		
Acute fatty liver of pregnancy	Nausea, vomiting, headache, abdominal pain, polyuria, polydipsia in the third trimester	New nausea and vomiting in the third trimester are not caused by hyperemesis gravidarum Women with AFLP are more unwell and often have associated renal impairment, coagulopathy, hypoglycemia, and preeclampsia
Hemolysis, elevated liver enzymes and low platelets syndrome	Hypertension, proteinuria, headache, epigastric pain, visual disturbance in the second or third trimester	Hypertension and proteinuria are predominant features
Hyperemesis gravidarum	Nausea and vomiting in the first trimester	Presentation in early pregnancy, abnormal liver function test resolves with successful treatment
Preexisting causes of hepatic impairment		
Viral hepatitis	Jaundice, nausea, vomiting, abdominal pain	Systemic symptoms, generally unwell, contacts
Primary biliary cirrhosis or primary sclerosing cholangitis	Pruritus, jaundice, lethargy, other autoimmune disorders	Symptoms before pregnancy; associated autoantibodies
Autoimmune hepatitis	Nausea, lethargy, jaundice, other autoimmune disorders	Symptoms before pregnancy; associated autoantibodies
Drug-induced liver injury	Pruritus, jaundice	Ingestion of drugs before onset of symptoms or biochemical abnormalities
Biliary obstruction	Abdominal pain, pale stools, dark urine	Liver ultrasound scan abnormalities
Venoocclusive disease	Abdominal pain, distension (ascites), jaundice, gastrointestinal bleeding	Thrombosis demonstrated on imaging, thrombophilia

SGA: small for gestational age; AFLP: acute fatty liver of pregnancy.

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